Original Article

Usefulness of serum fibrin degradation products and D-dimer levels as biomarkers to predict return of spontaneous circulation in patients with cardiopulmonary arrest on arrival: comparison with acid–base balance

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Aim: We evaluated the usefulness of fibrin degradation products and D-dimer levels in blood to predict return of spontaneous circulation in patients with cardiopulmonary arrest on arrival compared with anion gap and albumin-corrected anion gap.

Methods: We retrospectively reviewed the medical records of patients with cardiopulmonary arrest on arrival who had been transferred to the emergency department of our hospital in 2012. Patients were divided into two groups: patients with return of spontaneous circulation (ROSC(+) group), and those without (ROSC(–) group). The levels of anion gap, albumin-corrected anion gap, fibrin degradation products and D-dimer measured on arrival were compared between the two groups.

Results: Fifty-three patients could be analyzed. The anion gap and albumin-corrected anion gap levels were significantly better in the ROSC(+) group than in the ROSC(–) group (anion gap, 28.7 mmol/L [median] versus 39.1 mmol/L; albumin-corrected anion gap, 31.1 mmol/L versus 40.9 mmol/L). The fibrin degradation product and D-dimer levels were significantly lower in the ROSC(+) group than in the ROSC(–) group (fibrin degradation products, 32.1 μg/mL versus 157.4 μg/mL; D-dimer, 9.9 μg/mL versus 37.4 μg/mL). The area under receiver operating characteristic curves to evaluate the relationship with return of spontaneous circulation of anion gap, albumin-corrected anion gap, fibrin degradation products, and D-dimer were 0.664, 0.667, 0.714, and 0.707, respectively.

Conclusion: Fibrin degradation products and D-dimer levels might be more useful as predictors of return of spontaneous circulation than anion gap and albumin-corrected anion gap.

Key words: Albumin-corrected anion gap, anion gap, cardiopulmonary arrest on arrival, D-dimer, fibrin degradation products

INTRODUCTION

OUT-OF-HOSPITAL CARDIOPULMONARY ARREST (CPA) is one of the most serious problems in community and public health. At present, the 2010 guidelines of the Consensus on Science with Treatment Recommendations (CoSTR) of the International Liaison Committee on Resuscitation are followed widely all over the world with some modifications based on each local situation, and cardiopulmonary resuscitation (CPR) is generally carried out according to these guidelines.

Unfortunately, useful parameters that can predict whether a patient with CPA can achieve return of spontaneous circulation (ROSC) after effective CPR have not yet been established. In addition, the 2010 CoSTR guidelines do not show definite criteria for termination of CPR. Therefore, emergency room (ER) physicians sometimes encounter a situation in which they struggle to make a decision as to whether CPR should be terminated or not. Previously, we paid attention to anion gap (AG) and albumin-corrected anion gap (ACAG), which can be easily obtained in the ER, as predictors of ROSC in patients with CPA, and reported that both AG and ACAG were associated with ROSC in patients with CPA and that ACAG was a more useful parameter to predict

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Received 8 Sep, 2013; accepted 6 Mar, 2014; online publication 19 May, 2014

ROSC compared with AG.[1] However, we also reported that there were correlations between the injury severity score and the initial plasma fibrin degradation products (FDP) and D-dimer levels, and that FDP and D-dimer levels were useful parameters for initial evaluation of the severity of trauma and requirement of massive blood transfusion or mortality in trauma patients.[2] In addition, Szymanski *et al*. investigated to determine whether the serum D-dimer concentration on arrival was an independent predictor of all-cause mortality in non-traumatic patients with out-of-hospital cardiac arrest and they concluded that the D-dimer concentration was an independent predictor of all-cause mortality.[3]

In this study, we analyzed the relationships between the levels of AG, ACAG, FDP, or D-dimer and ROSC in patients with CPA, and investigated the usefulness of FDP and D-dimer levels to predict ROSC compared with AG and ACAG.

METHODS

WE RETROSPECTIVELY STUDIED patients who were transferred to the ER of our hospital and had CPA on arrival (CPAOA) from January 2012 to December 2012, and excluded traumatic etiology from this study.

Electrocardiographic monitoring on arrival at our hospital showed one among asystole, pulseless electrical activity, or ventricular fibrillation/pulseless ventricular tachycardia in those patients diagnosed as CPAOA. Cardiopulmonary resuscitation was carried out in conformity with the 2010 guidelines. All patients were injected with epinephrine only as a vasoconstrictive agent, and vasopressin was not injected during CPR in this series. Blood samples were collected from the femoral artery in all patients with CPA within at least 5 min after arrival and before ROSC. Arterial blood gas analysis was carried out with an ABL800 FLEX analyzer (Radiometer, Tokyo, Japan) and the levels of Na^+, K^+, Cl^-, and albumin were measured in our laboratory center on arrival at our hospital. The FDP and D-dimer levels were also measured in our clinical laboratory with the coagulating method, synthesized substrate assay, and immunoturbidimetric method using the CS-2000i system (Sysmex, Kobe, Japan).

Anion gap and ACAG were calculated using the following formulae:

$$\mathrm{AG\ (mmol/L)} = ([\mathrm{Na^+}] + [\mathrm{K^+}]) - ([\mathrm{Cl^-}] + [\mathrm{HCO_3^-}])^{4}$$

$$\mathrm{ACAG\ (mmol/L)} = [4.4 - \{\text{observed serum albumin (g/dl)}\}] \times 2.5 + \mathrm{AG}^{5,6}$$

Successful resuscitation was defined as detection of a pulse at the carotid artery, femoral artery, or radial artery under advanced CPR then maintenance of systolic pressure at ≥80 mmHg for 1 h with or without the use of a vasoconstrictive agent. We defined this situation as "ROSC(+)". Anything other than ROSC(+) described above was defined as "ROSC(−)". Patients were divided into two groups: the ROSC(+) group and the ROSC(−) group.

Statistical analysis

Data are shown as the mean ± standard deviation. Comparisons of each parameter between the ROSC(+) and ROSC(−) groups were carried out using the Mann–Whitney *U*-test, χ^2 analysis, and *t*-test. Receiver operating characteristic (ROC) curves were used to evaluate the efficacy for predicting ROSC with the Youden index to decide the cut-off point (the optimal cut-off point is the one that maximizes the sum of sensitivity and specificity used in the Youden index approach). SPSS Statistics 20 software (IBM, Tokyo, Japan) was used for statistical analyses. Statistical significance was assumed to be present at a $P < 0.05$.

RESULTS

THE TOTAL NUMBER of patients who were transferred to our hospital as CPAOA without traumatic etiology between January 2012 and December 2012 was 53. There were 40 patients with asystole, 12 with pulseless electrical activity, and 1 with ventricular fibrillation/pulseless ventricular tachycardia. There were 27 patients with cardiac etiology (including presumed cases), 12 patients with respiratory disease, 3 patients with cerebrovascular accident, and 9 with other etiology. Only one patient was injected with 1 mg epinephrine before arrival. Of the 53 patients, 20 patients had ROSC.

In the ROSC(+) group ($n = 20$), the male/female ratio and the mean age were 13/7 and 72.0 ± 15.0 years, respectively. Male/female ratio and the mean age in the ROSC(−) group ($n = 33$) were 13/20 and 66.2 ± 22.6 years, respectively. There were no significant differences in the male/female ratio or age between the two groups.

The amount of i.v. administered epinephrine was significantly lower in the ROSC(+) group; 3.4 ± 2.6 mg in the ROSC(+) group and 5.0 ± 2.6 mg in the ROSC(−) group ($P = 0.004$). The mean CPR duration was also significantly shorter in the ROSC(+) group than in the ROSC(−) group; 14.9 ± 9.8 min in the ROSC(+) group and 29.5 ± 15.2 min in the ROSC(−) group ($P \leq 0.001$). Finally, all patients in the ROSC(+) group died.

The levels of AG and ACAG are shown in Figure 1. The median AG was 28.7 (range, 18.1–50.8) mmol/L in the ROSC(+) group and 39.1 (range, 13.9–59.4) mmol/L in the ROSC(−) group (Fig. 1A). The median ACAG was 31.1

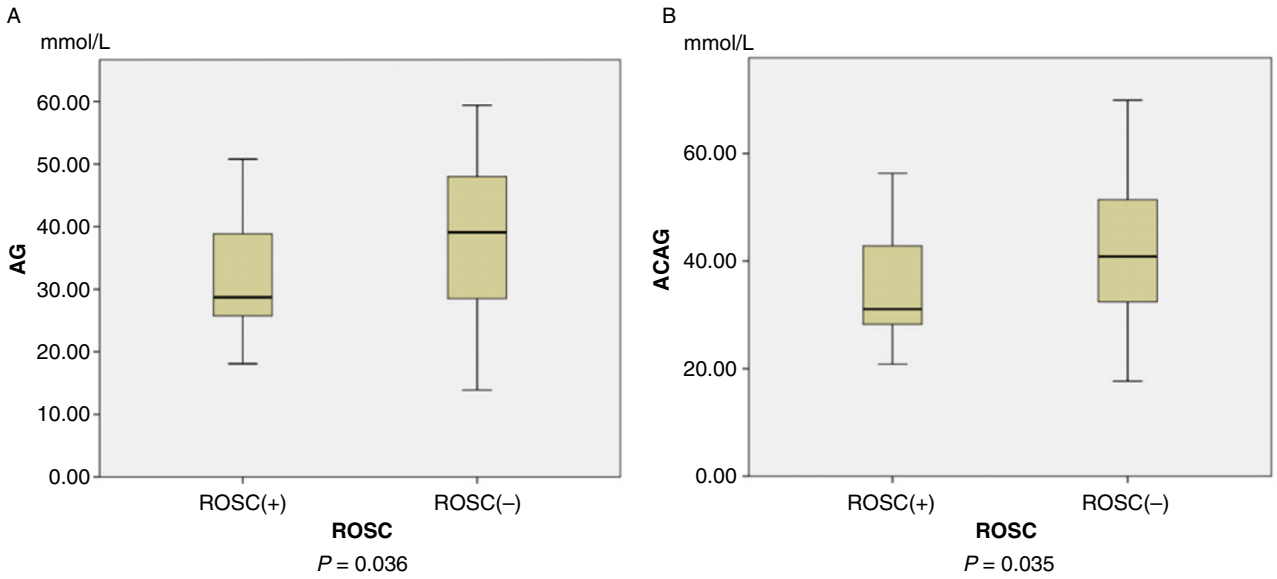

Fig. 1. Box plot of each parameter in patients with cardiopulmonary arrest who had return of spontaneous circulation (ROSC(+) group) and those who did not (ROSC(–) group). (A) Comparison of anion gap (AG). (B) Comparison of albumin-corrected anion gap (ACAG).

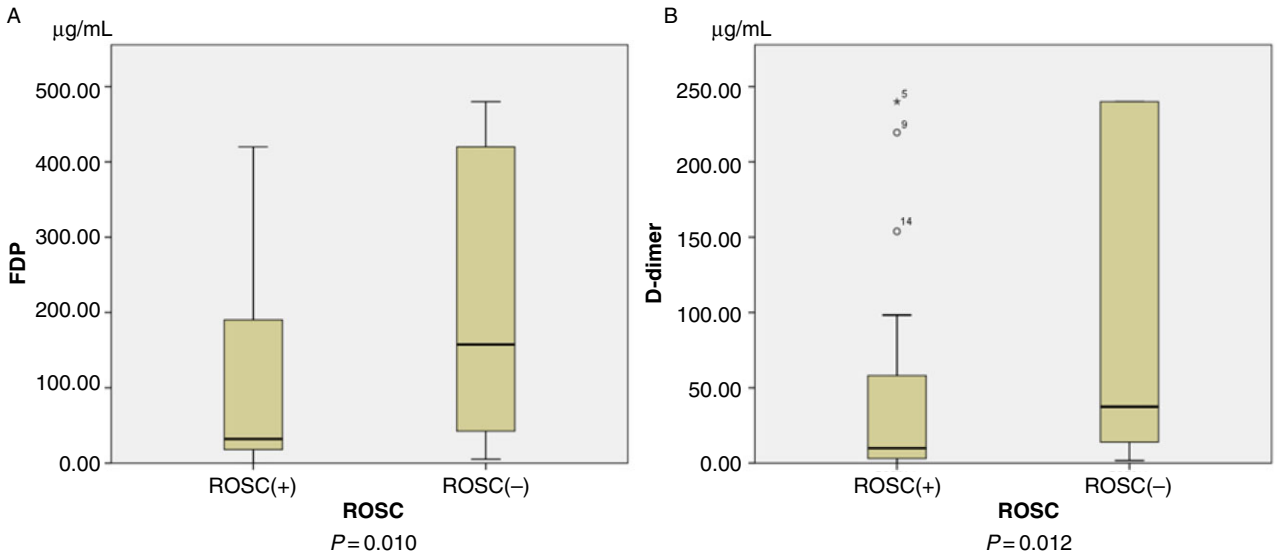

Fig. 2. Box plot of each parameter in patients with cardiopulmonary arrest who had return of spontaneous circulation (ROSC(+) group) and those who did not (ROSC(–) group). (A) Comparison of fibrin degradation products (FDP). (B) Comparison of D-dimer.

(range, 20.9–56.3) mmol/L in the ROSC(+) group and 40.9 (range, 17.7–69.9) mmol/L in the ROSC(−) group (Fig. 1B). Both AG and ACAG were significantly ($P < 0.05$) lower in the ROSC(+) group than in the ROSC(−) group.

The levels of FDP and D-dimer are shown in Figure 2. The median FDP was 32.1 (range, 0–420) μg/mL in the ROSC(+) group and 157.4 (range, 5.1–480) μg/mL in the ROSC(−) group (Fig. 2A). The median D-dimer level was 9.9 (range, 0–240) μg/mL in the ROSC(+) group and 37.4 (range, 1.7–240) μg/mL in the ROSC(−) group (Fig. 2B). Both FDP and D-dimer levels were significantly ($P < 0.05$) lower in the ROSC(+) group than in the ROSC(−) group.

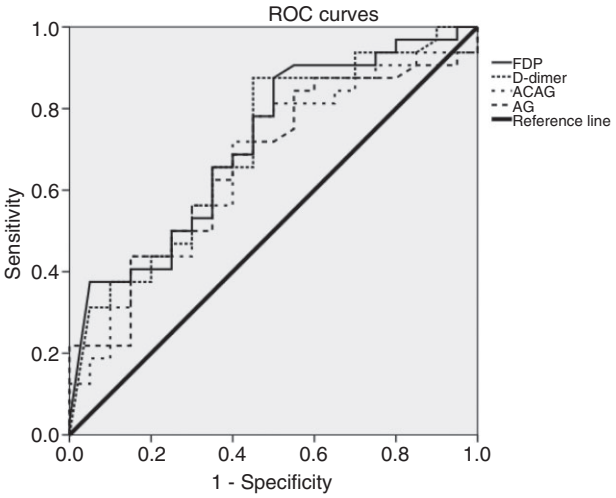

Fig. 3. Receiver operating characteristic (ROC) curves of parameters to predict whether a patient with cardiopulmonary arrest can achieve return of spontaneous circulation after effective cardiopulmonary resuscitation. ACAG, albumin-corrected anion gap; AG, anion gap; FDP, fibrin degradation products.

The ROC curves of each parameter are shown in Figure 3 and the areas under the ROC curve (AUC) for AG, ACAG, FDP, and DD are shown in Table 1. The AUCs of FDP and D-dimer were almost the same and higher than those of AG and ACAG. Cut-off points obtained with the Youden index are also shown in Table 1. The sensitivity of FDP was the same as that of D-dimer, and was higher than those of AG and ACAG. However, a significant difference was not recognized in specificity among AG, ACAG, FDP and D-dimer (Table 1).

DISCUSSION

THE OUTCOME OF out-of-hospital CPA patients is not yet satisfactory, despite widespread use of the 2010 CoSTR guidelines. It is difficult for emergency physicians to decide whether we should continue CPR because the 2010 guidelines do not show criteria to discontinue CPR and the judgment to continue CPR is currently entrusted to on-site physicians. Our opinion is that CPR should be continued as far as there is the possibility of ROSC. The establishment of parameters to predict ROSC in patients with CPA is important not only for the judgment of whether CPR should be continued but also for the medical economic side. In addition, those parameters should be able to be easily and quickly obtained in an emergency situation.

We focused on acid–base equilibrium to predict ROSC in patients with CPAOA in our previous study.[1] Anion gap is one of the most common parameters showing anion/cation balance. The normal range of AG is 8–16 mmol/L.[7] Anion gap in plasma is a time-honored diagnostic tool used in the evaluation of metabolic acidosis. However, the observed AG is often unreliable in detecting increased concentrations of these gap anions,[8] and Rocktaeschel *et al*.[9] insisted that the AG alone has limitations in critical illness. In particular, hypoalbuminemia, a common disturbance in hospitalized patients, can mask an increased concentration of gap anions by lowering the value of AG.[8,10] Hatherill and colleagues[5] insisted that ACAG was a more appropriate screening tool for the diagnosis of metabolic acidosis in the intensive care unit and ACAG should be calculated to screen for occult tissue anions in children with shock. Morris *et al*.[11] proposed ACAG-based techniques for bedside use in critically ill patients. Based on the above statement, we reported that both AG and ACAG were associated with ROSC and the relationship between ACAG and ROSC was stronger than that between AG and ROSC in CPAOA patients.[1]

D-dimer is a specific cross-linked fibrin derivative that is a product of the endogenous fibrinolytic degradation of fibrin. Both FDP and D-dimer are well-established markers of coagulation and their levels have been found to correlate with thrombosis.[12,13] Normal D-dimer levels could exclude deep vein thrombosis.[14] Recent reports suggest that a new purpose to measure coagulation markers is not only assess-

Table 1. Areas under receiver operating characteristic curves (AUC) and cut-off points of parameters to predict whether a patient with cardiopulmonary arrest can achieve return of spontaneous circulation after effective cardiopulmonary resuscitation

	AG	ACAG	FDP	D-dimer
AUC (95%CI)	0.664 (0.514–0.815)	0.667 (0.516–0.818)	0.714 (0.571–0.858)	0.707 (0.561–0.853)
Cut-off point	27.8 mmol/L	31.7 mmol/L	29.4 μg/mL	10.2 μg/mL
Sensitivity, %	84.4	78.1	87.5	87.5
Specificity, %	45.0	55.0	50.0	55.0

AG, anion gap; ACAG, albumin corrected anion gap; CI; confidence interval; FDP, fibrin degradation products.

ment for coagulopathy but also to diagnose or predict the outcome. For example, coagulation markers measured at arrival to the hospital are useful to detect hidden diseases such as aortic dissection[15] or to predict the outcome of patients with head injury[16–19] and to predict the amount of bleeding in trauma patients.[20] We reported that FDP and D-dimer levels of trauma patients at arrival were correlated with the injury severity score.[2] In addition, Szymanski *et al*. reported that the D-dimer concentration measured on arrival was an independent predictor of all-cause mortality in non-traumatic patients with out-of-hospital cardiac arrest.[3]

Taking those results into consideration, we focused our attention on acid–base equilibrium and markers of coagulation in patients with emergency situations. Few reports demonstrated coagulation of patients with CPAOA. Gando *et al*.[21] had mentioned that D-dimer and fibrinopeptide levels were higher in patients without ROSC than in patients with ROSC. They also reported that during and after CPR in patients with out-of-hospital cardiac arrest, massive fibrin generation with consecutive impairment of fibrinolysis was observed. Enhanced tissue factor expression results in distinct thrombin generation, followed by an increase in plasminogen activator inhibitor activity and subsequent inhibition of fibrinolysis.[21,22] Adrie *et al*.[23] reported that the D-dimer level measured after ROSC was higher in patients who died than in survivors and they thought that this was caused by a procoagulant pathway and inflammatory response that were activated by hypoperfusion of CPA.

The reports described above show the elevation of FDP/D-dimer in patients with CPA with/without ROSC; however, those authors did not have the perspective of FDP/D-dimer as predictors of ROSC and they did not mention the cut-off point for ROSC in patients with CPAOA. To our knowledge, this is the first report that mentions the cut-off points between ROSC and FDP/D-dimer. In addition, this is the first research study that describes the relationships between AC, ACAG, FDP, or D-dimer and ROSC in patients with CPAOA. The AUCs of FDP/D-dimer were larger than those of AC/ACAG, indicating that FDP and D-dimer might be better predictive factors of ROSC than AG and ACAG. Nevertheless, both AG and ACAG can be calculated with simple formulae and the data on AG and ACAG can be collected more quickly than FDP/D-dimer levels in many hospitals.

Limitations

This was a retrospective study, and the number of patients was not large. In addition, only CPAOA patients in whom blood gas analysis, FDP, and D-dimer levels in blood were examined, were included in this study. Further studies should be carried out in a multicenter setting.

CONCLUSION

FIBRIN DEGRADATION PRODUCT and D-dimer levels might be more useful as predictors of ROSC than AG and ACAG, although AG and ACAG values can be obtained more quickly than FDP and D-dimer levels in an emergency situation.

CONFLICT OF INTEREST

NONE.

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